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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,048	03/28/2007	Karl-Hermann Schlingensiepen	4052.003	4668

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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
09/18/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,048	SCHLINGENSIEPEN ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-45* is/are pending in the application.

4a) Of the above claim(s) *34-38 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-33 and 39-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 January 2008 and 28 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/21/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to comply*.

DETAILED ACTION

Election/Restrictions/Status

Applicant's election without traverse of "melanoma" as the type of cancer in the reply filed 7/13/2009 is acknowledged.

The previous Action acknowledged Applicant's election without traverse of Group I, claim(s) 23-34 and 38-45, drawn to a method for treating cancer, comprising administering at least one oligonucleotide, and to an antisense oligonucleotide and pharmaceutical composition thereof. Also acknowledged was Applicant's further election without traverse of "carcinoma," and with traverse of "TGF-beta 2" and "SEQ ID NO:30."

Claims 23-45 are pending.

Claims 34-38 and 45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/24/2008.

Claims 23-33 and 39-44 are examined herein.

Claim Objections

Claims 24 and 44 are objected to because of typographical (spelling) errors: "metasteses" and "metastase."

Specification/Sequence Compliance

Applicant's amendment to the specification and addition of an inadvertently omitted drawing filed 1/25/2008 is acknowledged. It is noted the omitted drawing is found in Provisional Application 60/558135 and is accepted pursuant to 37 CFR 1.57.

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The disclosure is objected to because of the following: This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The specification as filed does not comply with the requirements above, in particular 1.821(d) at least, because it contains nucleotide sequences of over 10 nucleobases each that are not identified by accompanying sequence identifiers.

For example, the sequences set forth at pages 47-80 are disclosed without corresponding SEQ ID NO: identifiers. This is but a sampling of the many sequences set forth in the instant application without SEQ ID NO: identifiers. Applicants are advised to review the entire application—claims, drawings, and specification—for complete compliance with the Sequence Rules.

Thus, the Examiner notes herein that the above listing of pages and figures which set forth examples in the specification of nucleotide sequences that require SEQ ID NO: is by way of illustration. In order to be fully responsive to this Office Action, Applicant should review this

application in its entirety to ensure compliance with the requirements of 37 CFR 1.821 through 1.825 and to make all appropriate corrections.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23-33 and 39-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13 and 16 of copending Application No. 11/647586. Although the conflicting claims are not identical, they are not patentably distinct.

The conflicting application claims an antisense oligonucleotide (SEQ ID NO:83) disclosed as useful for inhibiting the expression of TGF-β and for treating neurofibroma,

malignant glioma including glioblastoma, and skin carcinogenesis. Accordingly, it would have been immediately obvious to administer the antisense to a subject as now claimed, including such subjects having skin cancer such as melanoma. All effects inherent to the administration of the oligonucleotide would be obtained thereby, including those recited in the instant claims. It is noted the conflicting application does not claim an oligonucleotide identical to instant SEQ ID NO:30. However, the instant claims continue to recite several oligos that may be identical or patentably indistinct from conflicting SEQ ID NO:83. Applicant is in the best position to make that determination.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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Claims 23-33 and 39-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20-26 of copending Application No. 10/146058. Although the conflicting claims are not identical, they are not patentably distinct.

The conflicting application claims several different antisense oligonucleotides disclosed as useful for inhibiting the expression of TGF-β and for treating neurofibroma, malignant glioma including glioblastoma, and skin carcinogenesis. Accordingly, it would have been immediately obvious to administer the antisense to a subject as now claimed, including such subjects having skin cancer such as melanoma. All effects inherent to the administration of the oligonucleotide would be obtained thereby, including those recited in the instant claims. It is noted the conflicting application does not claim an oligonucleotide identical to instant SEQ ID NO:30.

However, the instant claims continue to recite several oligos that may be identical or patentably indistinct from those recited in the conflicting claims. Applicant is in the best position to make that determination.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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Claims 23-33 and 39-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-7, 18, 20-24 of copending Application No. 10/581547. Although the conflicting claims are not identical, they are not patentably distinct.

The conflicting application claims antisense oligonucleotides and pharmaceutical compositions thereof comprising sequences identical to those recited in the instant claims, including SEQ ID NO:30, for inhibiting the expression of TGF-β and for treating melanoma. Accordingly, it would have been immediately obvious to administer any of the antisense oligonucleotides to a subject as now claimed to subjects having melanoma. All effects inherent to the administration of the oligonucleotide would be obtained thereby, including those recited in the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-33 and 39-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because of the recitation "or its active derivative." One of skill in the art would not know the metes and bounds of the term because the specification has not clearly defined how and to what degree a compound can differ from the claimed compounds and still be considered an active derivative within the scope of the claims. The term reasonably embraces a multitude of structurally distinct nucleic acid-based compounds, including compounds comprising any type of non-nucleic acid element, group, or moiety, and the specification does not reasonably enable one of skill to envision the group of compounds specifically included or excluded by this limitation.

Correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23-33 and 39-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlingensiepen et al. (US Patent 6,455,689) "Antisense-oligonucleotides for transforming growth factor-β (TGF-β)" in view of:

1. Fakhrai et al. (US Patent 6,120,763)"Compositions and methods for enhanced tumor cell immunity in vivo";
2. Monia et al. (US 2004/0006030) "Antisense modulation of TGF-β2 expression"; and
3. Reed et al. (1994) "Expression of transforming growth factor-beta 2 in malignant melanoma correlates with the depth of tumor invasion. Implications for tumor progression" *Am J Pathol.* Jul;145(1):97-104.

Schlingensiepen et al. disclosed and claimed antisense oligonucleotides and chemically modified derivatives thereof for inhibiting the expression of TGF-β2 and treating various carcinomas, including skin carcinogenesis (see entire disclosure, including col. 6, lines 20-30). In one embodiment the antisense oligonucleotide recommended and claimed (SEQ ID NO:72) is identical to instantly recited SEQ ID NO:30 (col. 2). As evidenced by the instant claims, SEQ ID NO:30, and therefore SEQ ID NO:72, is an oligonucleotide that inhibits the formation of metastases and production of TGF-beta2.

It would have been obvious to use any of the anti-TGF-β oligonucleotides disclosed by Schlingensiepen et al. to treat melanoma (and consequently inhibit metastasis) in a subject in view of the fact that Schlingensiepen et al. specifically teaches the antisense are useful for treatment of skin carcinogenesis, given that melanoma was a well recognized form of skin carcinogenesis at the time of invention, and further given that Monia et al., Fakhrai et al., and Reed et al. taught the correlation between TGF-β2 expression/production and malignant melanoma and specifically recommended using antisense oligonucleotides to inhibit the expression of TGF-β and treat cancer.

For example, Fakhrai et al. disclose and claim a method for prolonging survival of a subject having melanoma, comprising administering to said subject a therapeutically effective amount of genetically modified cells containing a genetic construct expressing an antisense oligonucleotide that inhibits the expression of TGF-β, including TGF-β2 (see disclosure and claims).

Monia et al. disclosed methods and materials for making and administering nuclease resistant antisense oligonucleotides to inhibit the expression of TGF-β2 and thereby treat various

hyperproliferative diseases in a subject. Monia et al. taught the association between TGF-β2 expression and various forms of cancer, including melanoma, stating the prior art had disclosed that TGF-beta 2 was found to be expressed in all uveal melanomas tested (par. 12). It is taught the antisense oligonucleotides disclosed therein may be used in diagnostics, therapeutics, and prophylaxis, and that antisense oligonucleotides in general have been employed as therapeutic moieties in the treatment of disease states in animals and man. Antisense oligonucleotide drugs, including ribozymes, have been safely and effectively administered to humans and numerous clinical trials are presently underway. It is thus established that oligonucleotides can be useful therapeutic modalities that can be configured to be useful in treatment regimes for treatment of cells, tissues and animals, especially humans (par. 50).

Reed et al. suggested that TGF-beta 2 expression in malignant melanoma may be a critical event in the development of deep invasion and metastases in malignant melanoma.

Accordingly, the instantly claimed methods would have been prima facie obvious at the time of invention.

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Claims 23-33 and 39-44 are rejected under 35 U.S.C. 103(a) as being obvious over Schlingensiepen et al. (US 2007/0196269; 10/581547) and, in the alternative, Schlingensiepen et al. (US 2008/0214483; 11/647586), each independently in view of:

1. Schlingensiepen et al. (US Patent 6,455,689) "Antisense-oligonucleotides for transforming growth factor-β (TGF-β)" in view of:
2. Fakhrai et al. (US Patent 6,120,763) "Compositions and methods for enhanced tumor cell immunity in vivo";

3. Monia et al. (US 2004/0006030) "Antisense modulation of TGF-β2 expression"; and
4. Reed et al. (1994) "Expression of transforming growth factor-beta 2 in malignant melanoma correlates with the depth of tumor invasion. Implications for tumor progression" *Am J Pathol.* Jul;145(1):97-104.

The applied references each have a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Schlingensiepen et al. (US 2007/0196269) and Schlingensiepen et al. (US 2008/0214483) each disclosed antisense oligonucleotides and methods of use thereof within the scope of the instant claims for inhibiting TGF-β2 expression and treating skin carcinogenesis in a subject.

Prior art references 1-4 are relied on for the reasons given above in the rejection of the claims under 35 USC 103. As a whole the prior art reasonably suggested inhibiting the expression/production of TGF-β2 using antisense oligonucleotides to treat various forms of cancer, including melanoma, as implied by Schlingensiepen et al. in each of the applications above.

Accordingly, the instant methods would have been prima facie obvious at the time.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Primary Examiner, Art Unit 1635
September 15, 2009